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EXAMINER	
POPA, ILEANA	

ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/022,390	VEGA ET AL.	
	Examiner	Art Unit	
	Ileana Popa	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 July 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *45,46,62,70,78,94 and 96-104* is/are pending in the application.

4a) Of the above claim(s) *101-104* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *45,46,62,70,78,94 and 96-100* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in the prior Office action.

2. Claims 1-44, 47-61, 63-69, 71-77, 79-93, and 95 have been cancelled. Claims 45, 62, 96, and 97 have been amended. Claims 101-104 are new.

Election/Restriction

Applicant submits that, as amended, claim 45 and its dependent claims are not anticipated by the cited reference and therefore, the Examiner is required to search additional sequence species, beside the elected SEQ ID NO: 113, until art is found or until a reasonable number of species is searched.

It is noted that Applicant amended the claims reciting the different SEQ ID NO: species such that they are now dependent from claim 62. Since the generic claim 62 encompassing the genus is not allowable, the election and examination of the species is maintained.

Accordingly, new claims 101-104 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim.

Claims 45, 46, 62, 70, 78, 94, and 96-100 are under examination.

** It is noted that claims 45, 46, 62, 70, 78, 94, and 96-100 contain non-elected subject matter. Claims 45, 46, 62, 70, 78, 94, and 96-100 are examined to the extent that they read on the elected subject matter, i.e., the mutation identified in

claim 62 as "T to N at position 350 of SEQ ID NO: 747", represented by SEQ ID NO: 113.

Response to Arguments

Claim Rejections - 35 USC § 101

3. The rejection of claims 45, 46, and 62 under 35 U.S.C. 101 as being directed to non-statutory subject matter is withdrawn in response to Applicant's arguments and amendment to claim 46 filed on 07/09/2007. It is noted that, while the art teaches naturally-occurring AAV Rep variants with diminished activity, the art does not teach naturally-occurring AAV Rep variants with increased activity that results in increased viral production.

Claim Rejections - 35 USC § 112, 2nd paragraph

4. The rejection of claims 45, 46, 62, 70, 78, 94, and 96-100 under 35 U.S.C. 112, second paragraph, as being indefinite, is withdrawn in response to Applicant's amendment to claim 45, filed on 07/09/2007.

5. The rejection of claims 62, 70, 78, 94, 96, 99, and 100 under 35 U.S.C. 112, second paragraph, as being indefinite, is withdrawn in response to Applicant's amendment to the claims, filed on 07/09/2007.

6. The rejections of claims 96, 99, and 100 under 35 U.S.C. 112, second paragraph, as being indefinite, are withdrawn in response to Applicant's amendment to

the claims, filed on 07/09/2007.

Claim Rejections - 35 USC § 112, new matter

7. The rejection of claims 96, 99, and 100 under 35 U.S.C. 112, first paragraph, as introducing new matter, is withdrawn in response to Applicant's amendment to the claims, filed on 07/09/2007.

Claim Rejections - 35 USC § 112, written description

8. Claims 45, 46, 62, 70, 78, 94, and 96-100 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for the reasons of record set forth in the prior Office actions. Applicant's Applicant's arguments filed 07/09/2007 have been fully considered but they are not persuasive.

Applicant traversed the instant rejection on the grounds that the specification identifies and provides examples of 12 species of nucleic acids encoding mutant Rep proteins that, when expressed, result in higher AAV titers. Applicant argues that the specification provides detailed description of how to isolate and prepare additional species that have the required property. Applicant submits that, since the application is directed to methods for preparing proteins with predetermined properties, Applicant was in possession of the claimed genus. Applicant argues that the specification describes a representative number of species by actual reduction to practice, provides the sequences of such molecule and the corresponding positions in other AAV serotypes, and provides the relevant identifying characteristics of the claimed nucleic acid

molecules, i.e., modified nucleic acid molecules that encode Rep proteins resulting in increased AAV titer. Applicant argues that the application tested every amino acid locus to identify all whose changes result in a change in titer and therefore, the specification provides a detailed description of the relationship between the structure and function of Rep proteins, as assessed by the viral titer. Applicant asserts that, based on this property and using the methods as described, the application teaches how to identify additional species within the scope of the claims and how to assay combinations of mutations. Applicant argues that, since the specification exemplifies an entire genus with respect to one serotype and identifies the corresponding mutations in all other AAV serotypes, Applicant was in possession of the claimed subject matter as of the filing date of the instant application. Applicant submits that he is not required to provide a representative number of everything that is claimed, but rather show possession by providing identifying features common to all members. Therefore, Applicant requests the withdrawal of the rejection.

Applicant's arguments are acknowledged, however, the rejection is maintained for the following reasons:

Claims 45, 46, and 98 are drawn to nucleic acid molecules encoding any mutant AAV Rep protein, wherein the mutation(s) results in increased activity that translates into an increased viral titer. Claims 62, 70, 78, 94, and 96, 97, 99, and 100 are drawn to nucleic acid molecules encoding mutated AAV Rep, wherein the Rep proteins have one or more mutations, wherein the mutations comprise mutations selected from T350N, T462I, P497R/L/Y, T517N, G598D/S, and V600P in AAV-2 Rep78 or the corresponding

positions in the Rep proteins of the other serotypes; these mutations lead to increased Rep activity and increased viral titer. However, with the exception of the sequences disclosed mutations, the specification fails to describe additional representative species of the nucleic acids mentioned above. While it is true that the above mutations are expected to result in mutant Rep proteins with similar increased activity when applied the Rep proteins of other AAV serotypes (it is noted that the Rep proteins are highly conserved among the different serotypes), the claimed genus is much broader than this since it encompasses any other mutation(s) over protein lengths of approximately 620 amino acid residues, wherein the mutation(s) must result in increased activity. One skilled in the art would know that a change of even one amino acid residue in the claimed sequences could render an inactive protein or a protein with a diminished activity. It is noted that the art and the instant specification do teach that the majority of mutations in Rep protein sequence results in a protein with decreased activity or in a dominant negative Rep protein. Even in his arguments, Applicant admits that most of the mutations he tested did not result in a protein having an increased activity, as required by the instant invention. Applicant argues that the specification provides methods to mutate Rep and test the mutations or the combination of mutations; however, just by having a method to mutate and test does not mean that Applicant was in possession of the entire claimed genus, especially that, as indicated above, the majority of mutations does not render the desired activity. Even Applicant's argument that he tested substitution of every amino acid at every locus and identified only eight hits supports this assertion. It is also noted that the genus of mutations, as broadly

claimed, comprises mutations other than single amino acid substitutions, mutations such as substitutions of several amino acids, deletions, insertions, or combinations thereof. Applicant did not provide any example of such a mutant, wherein the mutant is more active than the wild type. The art clearly teaches that Rep proteins are divided into partially distinct functional domains that are spread throughout the protein length and that most mutations disrupt Rep function; therefore, one of skill in the art would know that not just any mutation would increase Rep activity. Additionally, the mere fact that one of skill in the art would require additional experimentation to identify such mutants is a proof that Applicant was not in possession of the claimed genus.

Based on these teachings, one of skill in the art would not recognize that, with the exception of T350N, T462I, P497R/L/Y, T517N, G598D/S, and V600P mutations in AAV-2 Rep78 or the corresponding positions in the Rep proteins of the other serotypes, Applicant was in possession of the entire claimed genus.

Claim Rejections - 35 USC § 102

9. The rejection of claim 94 under 35 U.S.C. 102(b) as being anticipated by Gavin et al. is withdrawn because the claim was inadvertently included in the instant rejection (see below).

** It is noted that claim 94 depends from the non-rejected claim 62, and not from the claims under rejection, i.e., claims 45 and 46.

10. Claims 45, 46, and 98 remain rejected under 35 U.S.C. 102(b) as being anticipated by Gavin et al. for the reasons of record set forth in the prior Office actions. Applicant's Applicant's arguments filed 07/09/2007 have been fully considered but they are not persuasive.

** It is noted that, in the non-final Office action of 01/09/2007 the Examiner inadvertently typed claim 94 instead of 98. The Examiner meant claim 98, since claim 98, and not claim 94, directly depends from the rejected claim 45.

Applicant traversed the instant rejection on the grounds that the claims are directed to a nucleic acid molecule encoding a mutant Rep protein that results in increased viral titer under standard conditions as compared to wild type Rep protein. Applicant argues that Gavin et al. teach a temperature sensitive (ts) mutant resulting in increased viral titers at 32°C, wherein the mutant is defective for replication under physiological conditions. Accordingly, Applicant argues, Gavin et al. do not teach a nucleic acid molecule encoding a mutant Rep with activity higher than that of the wild type Rep under standard conditions for the expression of the wild type protein. Therefore, Applicant requests the withdrawal of the rejection.

Applicant's arguments are acknowledged, however, the rejection is maintained for the following reasons:

Applicant did not provide any definition for standard condition used for wild type virus production. Moreover, the claims recite standard conditions and not physiological conditions. Gavin et al. compared titers for viruses comprising mutated and wild type Rep at 32°C, and therefore, this is considered the standard condition for wild type virus

production in their assay. Therefore, Gavin et al. teach all the limitation of the instant claims and anticipate the claimed invention.

New Rejections

Claim Rejections - 35 USC § 112, new matter

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 45, 46, and 98 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. 37 CFR 1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application". Specifically, the amendment to the claim to include the term "standard conditions for wild type virus production" is considered new matter.

Applicant submits that support for this amendment is found throughout the entire specification, which describes AAV preparation under such conditions for support. It is noted that the search of the specification failed to provide literal support for "standard conditions for wild type virus production". The Examiner could not find any teaching of AAV production under standard conditions.

MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. MPEP 2163.06 further notes "When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendments made to the disclosure".

Conclusion

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ileana Popa whose telephone number is 571-272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Ileana Popa, PhD

/Joseph Woitach/

Joseph Woitach

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